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ACUTE LOADING INJURIES AND THEIR RELATION TO POST-TRAUMATIC OSTEOARTHRITIS IN A PRECLINICAL MODEL

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Purpose: Up to 50% of knee injuries that result in tears of the ACL progress to post-traumatic OA (ptOA) within 10-15 years of the initial trauma. This represents an almost 5-fold increase in risk compared to non-injured joints, with current interventions (including surgical reconstruction) not significantly altering OA risk. Factors other than altered biomechanics may therefore play a significant role in disease development. Risk, rate of onset, and progression of ptOA may be linked to the trauma's impact severity and the joint structures affected both acutely and chronically. A better understanding of the interaction of these variables may improve prognostic capability and enable the development of specific treatments for injury management and disease prevention. In the present study we investigated the relationships between age, gender, body mass, joint load, ACL rupture, and ptOA pathology using a murine model of non-surgical ACL rupture.
Methods: ACL injury was induced by a single, axial compressive load to the flexed knee of the mouse. At the peak load, 10-15 seconds of sustained compression was applied before release. An initial cadaveric study assessed ACL failure loads over a range of mouse biometrics (9-52 week old, male and female C57BL-6, n=164). The failure load was determined from force-displacement curves and the mode of failure by microscopic evaluation. The potential predictors of these outcomes were assessed using mixed model linear regression and mixed model multinomial logistic regression. A subsequent in vivo study loaded the knees of anaesthetised mice (10-12 week, male C57Bl-6) to either failure or 55% of the mean failure. Joint pathology was assessed histologically at 2 or 4 weeks post-injury (n=7) in both the medial and lateral compartments.
Results: In the cadaveric study, damage induced by loading was largely restricted to the ACL with little evidence of injury to other joint tissues. The ACL was consistently ruptured but the mode of failure varied between specimens. Ruptures occurred towards the femoral insertion with 16% of tears entirely midsubstance, 35% total avulsion fractures and 49% demonstrating a mixture of the two. Logistic regression determined that there was no effect of age, mass, rupture load or joint stiffness on the mode of failure. However, when comparing males and females with avulsion fractures, the relative risk for females was 7.11 (95% CI [1.36 37.07]). The ACL rupture load itself was demonstrated to have a positive association with mass ($p < 0.001$) but not age or gender when correcting for other covariates.
In the in vivo study, complete ACL rupture resulted in significant femorotibial OA pathology, particularly towards the posterior region and greatest in the medial compartment. At 2 weeks substantial synovitis, tibio-femoral cartilage erosion and structural damage to the medial meniscus were evident. By 4 weeks cartilage erosion progressed and subchondral bone sclerosis, osteophytes and enthesophytes developed. In contrast, sub-failure loading of the knee resulted in only mild OA pathology. In these knees the ACL remained intact and there was no evidence of synovitis or osteophyte development. There was mild cartilage damage (unlike ACL failure this was similar in medial and lateral compartments) with significant progression from 2 to 4 weeks. A very localised subchondral bone remodelling response was also evident posteriorly in the tibia.
Conclusions: In this model ACL failure loads have been established for a range of mouse biometrics and were shown to be independent of the age and sex of the mouse. In vivo, complete ACL failure results in the rapid onset of pathology with a clinically relevant pattern of OA change in all other joint tissues. At the early time points examined in this study, mechanical loading alone (no ACL rupture) induces mild changes largely restricted to the cartilage, although this may progress further given more time. Comparisons with other loading regimes and surgical models of ptOA may further illuminate the complex interactions that occur between different joint tissues and risk factors for ptOA.

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THE RELATIONSHIP BETWEEN LOWER EXTREMITY STRENGTH AND FUNCTION WITH TIBIOFEMORAL JOINT SPACE WIDTH FOLLOWING ACL INJURY AND SURGICAL RECONSTRUCTION

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Purpose: Persistent strength decrements about the thigh have been implicated in the onset and progression of post-traumatic osteoarthritis (PTOA) following anterior cruciate ligament rupture and surgical reconstruction (ACLR), however, this relationship has not been thoroughly evaluated. Consequently, the purpose of this study was to assess the relationship between lower extremity strength, function, and patient- and clinically-oriented outcomes with tibiofemoral joint space width (JSW) following ACL injury and surgical reconstruction, compared to healthy controls.
Methods: Sixty-five acute, ACL-injured subjects and 32 healthy controls from two research cohorts were evaluated at pre-surgical baseline, and 1, 2, 4, and 7 years post-ACLR. Isokinetic knee strength (60 and 180°/sec), single leg hop, orthopedic knee evaluation (IKDC 2000), anterior-posterior tibiofemoral laxity (KT1000), activity level (Tegner Activity Score), Knee Injury and Osteoarthritis Outcomes Score (KOOS) were evaluated. At final follow-up, JSW was calculated from standing, fluoroscopy-assisted metatarsal phalangeal view knee x-rays and compared bilaterally. ACLR subjects were categorized into Narrow, or Normal JSW groups if their injured-to-uninjured JSW values were less than, or within the 95% confidence interval of control subjects respectively. Relationships between outcomes and JSW groups were evaluated using data from all available time points using multilevel regression, and Kruskal-Wallis tests for between-group comparisons.
Results: Subject demographic data is presented in Table 1. At final follow-up, 49 ACLR subjects (75%) were allocated to the normal JSW group (ACLR-Normal), and 16 (25%) to the narrowed JSW group (ACLR-Narrow). At baseline, all strength values for ACLR subjects were significantly lower than controls ($p \leq 0.01$), while the ACLR-Narrow group had lower extension strength at 60 and 180°/sec ($p = 0.02$ and 0.01 respectively, Table 2), compared to ACLR-Normal subjects. At final follow-up, 60°/sec extension strength deficits persisted in the ACLR-Narrowed group compared to the ACLR-Normal group ($p = 0.04$) and controls ($p = 0.03$) (Table 3). Flexion strength was also significantly lower in ACLR-Narrow subjects compared to the ACLR-Normal group at 60 and 180°/sec ($p = 0.03$ and 0.04 respectively) at final follow-up, as was the Single Leg Hop test ($p = 0.05$) (Table 3). Between group comparisons of clinical-oriented outcomes and final follow-up Tegner activity score are presented in Table 4. There were no significant IKDC or KT1000 value differences between ACLR-Narrow subjects compared to the Normal group at baseline or final follow-up. However, there were significant activity level differences between Narrow and Normal group subjects, with ACLR-Normal group subjects having higher activity levels ($p = 0.02$). There were significant differences between all KOOS subscales between Control subjects and both ACLR groups at baseline and final follow-up (Table 5). There were no significant KOOS subscale differences between ACLR groups at baseline, however, ACLR-Narrow group subjects reported more pain ($p = 0.03$) and lower quality of life ($p = 0.03$) compared to ACLR-Normal subjects at final follow-up.
Conclusions: ACLR-Narrow subjects had significantly lower pre-surgical extension strength, which persisted through final follow-up compared to ACLR subjects with normal JSW. At final follow-up, ACLR-Narrow subjects also had lower extension and flexion strength, and single leg hop scores compared to the ACLR-Normal group. Additionally, ACLR-Narrow subjects had significantly lower activity level, increased pain, and lower quality of life compared to the ACLR-Normal group at final follow-up. This study demonstrates a significant relationship between decreased lower extremity strength and function with narrowed JSW following ACL injury and surgical reconstruction.

Table 1
Subject Anthropometric Data.

	Baseline Age (yrs) (SD)	Baseline BMI (SD)	Pre-Injurv Tegner Score (SD)
Control (N=32)	26.7 (6.6)	23.4(3.3)	6.2(1-3)
ACLR-Norraal (N=49)	27.4(11.0)	25.7(5.3)	4.0(2.2)
ACLR-Narrow (N=16)	31.9(11.2)	24.8(2.6)	3.5(1.7)

Table 2
Results of Between-Group Multilevel Regression Comparisons (p-values).

Isokinetic Test (direction & velocity)	Between-Group Baseline Strength Comparisons			Between-Group Strength Change Over Time (slope) Comparisons		
	Control vs ACLR-Normal	Control vs ACLR-Narrow	ACLR-Normal vs ACLR- Narrow	Control vs ACLR-Normal	Control vs ACLR-Narrow	ACLR-Normal vs ACLR- Narrow
Extension 60	**<0.0001**	**<0.0001**	**0.02**	**0.0008**	**0.002**	0.85
Extension 180	**<0.0001**	**<0.0001**	**0.01**	**0.007**	**0.002**	0.23
Flexion 60	**0.0002**	**0.002**	0.86	**0.0007**	**0.02**	0.28
Flexion 180	**0.0002**	**<0.0001**	0.08	**0.003**	**0.01**	0.89
Ext/Flex 60	**<0.0001**	**<0.0001**	0.32	0.61	0.92	0.39
Ext/Flex 180	**0.02**	**0.01**	0.29	0.89	0.79	0.85
Single Leg Hop (inj/uninj)	**0.002**	**<0.0001**	0.06	**0.03**	**0.03**	0.87

Table 3
Strength Comparisons by JSW Group at Final Follow-Up.

Isokinetic Test	Mean Side-to-Side Percent value (% inj vs normal)			Between Group Comparisons (p-values)		
	Control	KL Grade 0	KL Grade 1/2	Control vs KL grade 0	Control vs KL Grade 1/2	KL Grade 0 vs KL Grade 1/2
Extension 60°/sec	98.8	94.2	91.6	0.33	0.09	0.25
(SD)	(11.6)	(13.0)	(7.6)			
Extension 180°/sec	101.6	95.7	95.7	0.03	0.30	0.70
(SD)	(12.6)	(10.8)	(8.6)			
Flexion 60°/sec	94.7	98.6	99.1	0.07	0.07	0.74
(SD)	(12.8)	(11.8)	(7.2)			
Flexion 180°/sec	97.9	98.1	99.8	0.72	0.47	0.74
(SD)	(9.4)	(10.6)	(9.4)			

Extension to Flexion Ratio	Injured Knee Ext:Flexion Ratio			Between Group Comparisons (p-values)		
Ext:Flex 60°/sec	1.7	1.5	1.5	**0.004**	**0.02**	0.35
(SD)	(0.2)	(0.2)	(0.2)			
Ext:Flex 180°/sec	1.4	1.3	1.3	0.15	0.15	0.67
(SD)	(0.3)	(0.2)	(0.2)			
Single Leg Hop	99.3	97.6	98.7	0.36	0.66	0.87
(SD)	(6.7)	(8.2)	(9.3)			

Table 4
Between Group Comparisons of Clinically-Oriented Outcomes.

	Baseline						Final Follow-up					
	Mean Scores (sd)			Baseline Between Group Comparisons			Mean Scores (sd)			Final Follow-Up Between Group Comparisons		
	Cont	Norm	Narrow	Control vs Norm	Control vs Narrow	Normal vs Narrow	Cont	Norm	Narrow	Control vs Norm	Control vs Narrow	Normal vs Narrow
IKDC Objective	3.8 (0.4)	2.4 (0.9)	2.8 (1.1)	**<0.0001**	**0.0005**	0.20	3.8 (0.4)	3.1 (0.6)	3.0 (0.7)	**<0.0001**	**<0.0001**	0.52
KT 1000 (Norm − Inj)	-0.6 (1.8)	-2.4 (3.0)	-3.3 (4.4)	**0.007**	0.06	0.77	-0.2 (2.0)	-3.1 (2.2)	-3.4 (2.7)	**<0.0001**	**0.002**	0.86
Tegner	N/A	N/A	N/A	N/A	N/A	N/A	5.8 (1.7)	6.5 (1.7)	5.3 (1.3)	0.07	0.48	**0.02**

Table 5
Between Group Comparisons of Knee injury and Osteoarthritis Outcome Score (KOOS).

	BASELINE						FINAL FOLLOW-UP					
	Mean Scores (sd)			Between Group Comparisons			Mean Scores (sd)			Between Group Comparisons		
	Cont	Norm	Narrow	Control vs Norm	Control vs Narrow	Normal vs Narrow	Cont	Norm	Narrow	Control vs Norm	Control vs Narrow	Normal vs Narrow
Pain	99.4 (1.7)	77.4 (13.2)	71.0 (11.3)	**<0.0001**	**<0.0001**	0.07	99.6 (1.0)	94.7 (8.5)	92.2 (5.3)	**0.0003**	**<0.0001**	**0.03**
Quality of Life	99.4 (2.5)	41.0 (22.5)	28.5 (14.8)	**<0.0001**	**<0.0001**	0.06	98.4 (3.9)	87.5 (13.2)	78.4 (15.1)	**<0.0001**	**<0.0001**	**0.03**
Activities of Daily Living	99.9 (0.6)	87.9 (11.8)	85.6 (9.4)	**<0.0001**	**<0.0001**	0.16	99.9 (0.6)	98.2 (3.5)	97.7 (4.8)	**0.005**	**0.01**	0.91
Symptoms	97.7 (3.7)	68.6 (15.5)	61.8 (19.0)	**<0.0001**	**<0.0001**	0.23	98.0 (4.2)	89.3 (11.7)	89.1 (10.3)	**0.0001**	**0.0002**	0.67
Sports	99.5 (1.5)	53.7 (25.2)	40.6 (26.6)	**<0.0001**	**<0.0001**	0.09	99.1 (2.4)	90.1 (11.8)	88.0 (13.1)	**<0.0001**	**0.0001**	0.56